

Appl. No. 09/592,436
Amdt. Dated March 3, 2004
Reply to Office action of December 3, 2003

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A method of analyzing a substance, the method comprising:

- (1) creating a stream of ions in said substance and supplying the stream of ions to a mass selection device;
- (2) transmitting from said mass selection device a stream of precursor ions of a selected mass to charge ratio of interest ~~from said mass selection device~~;
- (3) supplying the stream of precursor ions and a collision gas to a multipole and providing an RF signal to the multipole, whereby the multipole functions as a collision cell;
- (4) fragmenting said precursor ions in the RF multipole by collisions with the gas molecules, in order to form primary fragment ions;
- (5) supplying additional alternating current to the multipole at a frequency selected to cause resonance excitation of a desired primary fragment ion mass-to-charge ratio, whereby ions with said desired primary fragment ion mass-to-charge ratio are excited and undergo collisions with the gas molecules causing production of secondary fragment ions;
- (6) modulating the alternating current signal applied in step (5) whereby periods in which said alternating current signal is applied alternate with periods in which the alternating signal is not applied;
- (7) detecting the ion signal after fragmentation with a mass spectrometer and collecting one set of data for one spectrum, representative of the ion spectrum when the

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alternating current signal is applied and another set of data for another spectrum, representative of the ion spectrum when the alternating current signal is not applied;

whereby said other spectrum can be subtracted from said one spectrum, to generate a subtracted spectrum showing the secondary fragment ions without the presence of the primary fragment ions except for any said primary fragment ions which are generated by step (5).

Claim 2 (previously presented): A method as claimed in claims 1 or 21, further including the step of processing the data sets by applying statistical analysis to reject spectra having statistically insignificant variations in the ion signal.

Claim 3 (original): The method as claimed in claim 2, wherein the statistical analysis is implemented in a software program and performed automatically.

Claim 4 (original): The method as claimed in claim 3, wherein the statistical analysis is performed in real time so that spectra having statistically insignificant variations in the ion signal are not displayed.

Claim 5 (previously presented): A method as claimed in claims 1 or 21, wherein, said multipole is a quadrupole.

Claim 6 (original): A method as claimed in claim 5, which includes applying the alternating current signal at a frequency that excites the desired primary fragment ion.

Claim 7 (canceled)

Claim 8 (previously presented): A method as claimed in claim 21, which includes providing a potential difference between the mass selection device and the collision cell,

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to accelerate the precursor ions into the collision cell, whereby the precursor ions gain sufficient velocity to collide with the collision gas to cause fragmentation, and wherein step (5) comprises applying an alternating current signal to excite the desired primary fragment ions.

Claim 9 (previously presented): A method as claimed in claims 21 or 8, which includes applying a second alternating current signal to the quadrupole rod set, to excite the secondary fragment ions generated in step (5), thereby to generate tertiary fragment ions and wherein step (6) comprises modulating the second alternating current signal.

Claim 10 (previously presented): A method as claimed in any one of claims 1, 21, or 8, which includes subtracting said one spectrum from the other spectrum to obtain a subtracted spectrum.

Claim 11 (original): A method as claimed in claim 9, which includes subtracting said one spectrum from said other spectrum to obtain a subtracted spectrum.

Claim 12 (original): A method as claimed in claim 10, which includes, for each peak, recording a plurality of data points encompassing the peak, and calculating a significance factor equation:

$$|T| = \text{Sig} = \frac{\left| \text{detected ion signal, alternating current on} - \text{detected ion signal, alternating current off} \right|}{\sqrt{\sigma^2 \text{ alternating current on} + \sigma^2 \text{ alternating current off}}}$$

and determining from the values of $|T|$ of the ion signal whether the detected ion signal with alternating current on created ions that significantly contributed to said peak.

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Claim 13 (previously presented): A method as claimed in claims 21 or 8, which includes applying a plurality of steps of selecting a desired fragmentation and applying an alternating current signal to generate additional fragment ions, wherein step (6) comprises modulating the last applied alternating current signal, whereby in step (7) said one spectrum includes said additional fragment ions formed by said last applied alternating current signal and said other spectrum comprises ions generated without application of said last applied alternating current signal.

Claim 14 (currently amended): An apparatus, for analyzing a substance by resonance excitation of selected ions and selective collision-induced dissociation, the apparatus comprising:

an ion source for generating a stream of precursor ions;

a mass selection device for receiving the stream of ions and transmitting a stream of precursor ions of a selected mass to charge ratio of interest;

a collision cell, including a multipole, for receiving the stream of precursor ions and provided with a collision gas, for collision-induced dissociation between the precursor ions and the buffer gas;

a power supply connected to the multipole for generating an RF field in the multipole for guiding fragment ions produced by the collision-induced dissociation between the precursor ions and the buffer gas and for applying an additional alternating current field at a frequency selected to excite a desired ion;

a modulation means connected to the power supply, for modulating the alternating current signal, whereby periods in which said alternating current signal are applied alternate with periods in which the alternating current signal is not applied.

Claim 15 (previously presented): An apparatus as claimed in claim 14, which additionally includes a detector for detecting fragment ions exiting the collision cell, a switch connected to the detector, two data storage devices connected to the switch, and a connection between the modulation control unit and the switch, whereby the switch

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switches detected data for periods when the alternating current signal is applied to one data storage device and collected data for periods when the alternating current signal is not applied to the other storage device.

Claim 16 (previously presented): An apparatus as claimed in claim 30, which includes a second power supply connected to the quadrupole rod set, a second modulation unit connected to the second power supply and also to the switch, before applying a second alternating current signal, for excitation of a second ion.

Claim 17 (canceled)

Claim 18 (original): An apparatus as claimed in claim 16, which includes a final mass analysis section, including the detector, for analyzing fragment ions from the collision cell.

Claim 19 (previously presented): An apparatus as claimed in claim 18, wherein the final mass analysis section comprises one of:

- a scanning mass analyzer and a detector; and
- a time-of-flight device, including the detector for providing a small spectrum.

Claim 20 (canceled)

Claim 21 (currently amended): A method as claimed in claim 1, wherein the mass selection device performs a mass analysis to select the [[a]] precursor ion mass to charge ratio of interest.

Claim 22 (previously presented): A method as claimed in claim 21, wherein the mass selection device is a multipole.

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Claim 23 (previously presented): A method as claimed in claim 21, wherein the mass selection device is a quadrupole.

Claim 24 (previously presented): A method as claimed in claim 2, which includes subtracting said one spectrum from the other spectrum to obtain a subtracted spectrum.

Claim 25 (previously presented): A method as claimed in claim 3, which includes subtracting said one spectrum from the other spectrum to obtain a subtracted spectrum.

Claim 26 (previously presented): A method as claimed in claim 4, which includes subtracting said one spectrum from the other spectrum to obtain a subtracted spectrum.

Claim 27 (previously presented): A method as claimed in claim 24, which includes, for each peak, recording a plurality of data points encompassing the peak, and calculating a significance factor equation:

$$|T| = \text{Sig} = \frac{|\text{detected ion signal, alternating current on} - \text{detected ion signal, alternating current off}|}{\sqrt{\sigma^2 \text{ alternating current on} + \sigma^2 \text{ alternating current off}}}$$

and determining from the values of $|T|$ of the ion signal whether the detected ion signal with alternating current on created ions that significantly contributed to said peak.

Claim 28 (previously presented): A method as claimed in claim 25, which includes, for each peak, recording a plurality of data points encompassing the peak, and calculating a significance factor equation:

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$$|T| = \text{Sig} = \left| \frac{\text{detected ion signal, alternating current on} - \text{detected ion signal, alternating current off}}{\sqrt{\sigma^2 \text{ alternating current on} + \sigma^2 \text{ alternating current off}}} \right|$$

and determining from the values of $|T|$ of the ion signal whether the detected ion signal with alternating current on created ions that significantly contributed to said peak.

Claim 29 (previously presented): A method as claimed in claim 26, which includes, for each peak, recording a plurality of data points encompassing the peak, and calculating a significance factor equation:

$$|T| = \text{Sig} = \left| \frac{\text{detected ion signal, alternating current on} - \text{detected ion signal, alternating current off}}{\sqrt{\sigma^2 \text{ alternating current on} + \sigma^2 \text{ alternating current off}}} \right|$$

and determining from the values of $|T|$ of the ion signal whether the detected ion signal with alternating current on created ions that significantly contributed to said peak.

Claim 30 (previously presented): An apparatus as claimed in claim 14, wherein the multipole is a quadrupole rod set.

Claim 31 (previously presented): An apparatus as claimed in claims 14 or 30, wherein the mass selection device is a multipole.

Claim 32 (previously presented): An apparatus as claimed in claims 14 or 30, wherein the mass selection device is a quadrupole.